REMARKS

This responds to the Office Action mailed on November 4, 2008.

Claims 39 and 40 are added. Accordingly, claims 2, 4, 8-10, 24-39 and 40 are now pending in the application.

Claim 40 defines the immune response as cytotoxic T cell mediated cell killing. Support for generating an immune response that involves cytotoxic T cell mediated cell killing can be found throughout the specification as filed, for example, at page 9, lines 1-31; at page 10, lines 21-29 and in the Examples (e.g., Example 2).

Claims 39 and 40 recite that the cytotoxic T cell is specific to said antigenic peptide or a part thereof. Support for generating such a specific cytotoxic T cell response that is specific to the antigenic peptide can be found throughout the specification as filed, for example, at page 13, lines 14-20 and in the Examples (especially Example 2, which discloses MART-1 specific cytotoxic T cells (see lines 26-27 on page 21)).

Claim 2 is amended. In particular, the phrase "by a class I MHC molecule" has been deleted from claim 2.

Applicants submit that no new matter has been added to the application.

§112 Rejections of the Claims

Claims 2, 4, 8-10, 24-38 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Examiner alleges that the specification does not enable the claimed methods directed to expressing a molecule on a cell.

However, the evidence of record clearly shows presentation of peptide antigens on the surface of cells subjected to the methods of the invention, and killing of those cells by cytotoxic T cells (one type of immune response). In particular, Applicants have provided data explicitly showing that cell killing by cytotoxic T cells occurs only when the cytotoxic T cell recognizes a previously internalized antigenic peptide on the surface of a cancer cell (see Example 2). These data also demonstrate that methods of the invention achieve presentation of sufficient antigenic peptide to allow recognition and cytotoxic T cell mediated cell killing of the cancer cells that internalized and presented the peptide on their cell surface (FIG. 3).

Contrary to the Examiner's allegations, use of antigen presenting cells was not required for such a cytotoxic T cell response. Instead, FM3 melanoma cells clearly displayed the MART-1 peptide when treated as recited in Applicants' claims (see Example 2 and the numerous responses previously filed with the Patent Office). Moreover, sufficient MART-1 peptide must have been displayed on the cell surface by MHC class I proteins because the cancer cells were killed by cytotoxic T cells (FIG. 3) and, as the Examiner knows, MHC class II proteins are not necessarily found on cancer cells.

Example 2

The Examiner again criticizes Example 2. According to the Examiner, the CTLs employed are primed/activated CTLS and are not representative of the generation or stimulation of an immune response. The Examiner cites Janeway again as alleged evidence that one of the fundamental rules of cellular immunology is the generation of an immune response from naïve T cells requires professional antigen presenting cells.

However, cancer antigens displayed on the surface of cancer cells commonly give rise to an immune response. For example, an article by Ditzel et al. (Cancer Research 53: 5920-28 (1993), hereinafter, "Ditzel") teaches an immune response against a cancer antigen that was generated in a patient with colon cancer.

> COU-1, a human IgM Mab, is secreted by the B9165 cell line, derived from fusion between the human fusion partner WI-L2-729-HF2 and lymphocytes obtained from a mesenteric lymph node of a patient with rectal cancer. [Citations omitted.] Ditzel, page 5920, right column.

Therefore, the Ditzel antibody, which is directed to the antigen displayed on colon cancer cells, was isolated by collecting lymphocytes from the lymph node of the patient and fusing those lymphocytes with an appropriate immortalized cell line (human WI-L2-729-HF2 cells). Ditzel goes on to disclose that the antibody reacts with breast, ovarian, and gastric adenocarcinomas (Ditzel, page 5920, right column; see also Ditzel, Figs. 2 and 5). Therefore, the Ditzel antibody

was originally generated against cancer antigens that are cell-bound, i.e. the cancer cells presented antigen to which an immune response (antibody production) was generated.

Accordingly, the Examiner's hypothesis that only antigen presenting cells can be used in the practice of the invention to generate an immune response is disproven. Applicants submit that the Examiner has therefore failed to make a prima facie case that Applicants' specification lacks enablement.

Controls for Example 2

The Examiner continues to assert that the controls for Example 2 are inadequate.

However, this is also incorrect -- a no-light control was used and when no light is used little or no photo-internalization of the MART-1 peptide occurs, and little cell death is observed after exposure to cytotoxic T cells (Fig. 3). Moreover, increased light exposure leads to increased uptake and display of the MART-1 peptide, which then leads to increased killing by the cytotoxic T cells. This is an internal control.

Furthermore, a Declaration by Anders Høgset (dated November 13, 2002) was previously submitted in which the experiment reported in Example 2 was repeated with additional controls. In particular, the experiment was conducted with and without the MART-1 peptide. Thus, Applicants have provided at least two types of controls with respect to the experiments described in Example 2.

Applicants further remind the Examiner that he has previously indicated that Example 2 is enabled (October 24 2003 Official Action at page 2; August 23 2004 Official Action at page 4; April 1 2005 Official Action at page 3). Applicants submit that the Examiner has therefore failed to make a prima facie case that Applicants' specification lacks enablement.

Photochemical Internalization Agents

The Examiner alleges that the specification only discloses actual use of ALPcS2a and TPPS2a as photochemical internalization agents. However, references that are available in the art indicate that all types of photosensitizing agents are useful for internalization of proteins and peptides. For example, U.S. Patent 7,223,600 explicitly teaches that "di- and tetra-sulfonated aluminum phthalocyanine (e.g. AlPcS2a), sulfonated tetraphenylporphines (TPPSn), nile blue,

chlorin e6 derivatives, uroporphyrin I, phylloerythrin, hematoporphyrin and methylene blue which have been shown to locate in endosomes and lysosomes of cells in culture." See, col. 6, lines 46-57. These photosensitizers are therefore suitable as photosensitizing agents for use in the invention.

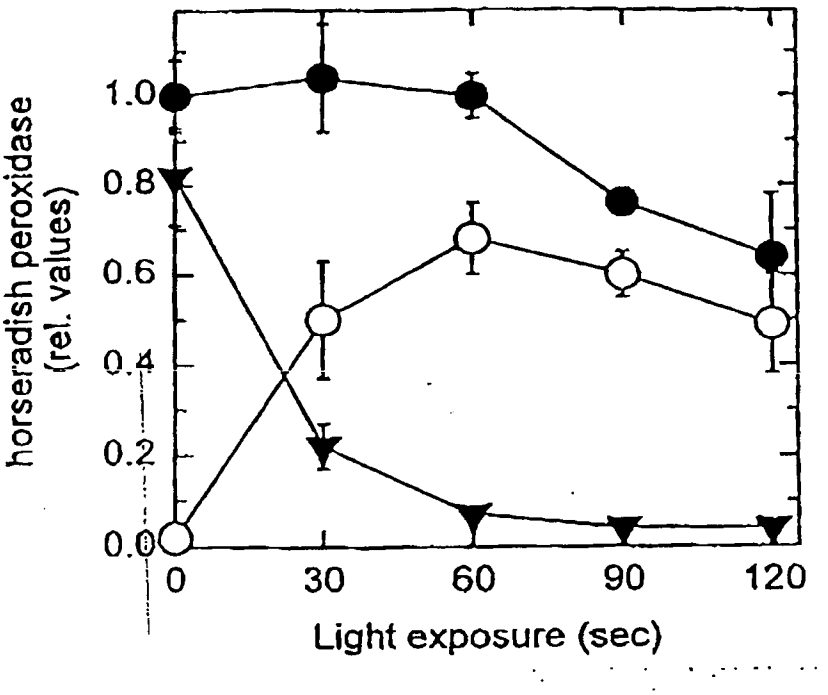
Moreover, the level of skill in this field is high. The invention is concerned with the application of a known technique to a new end use based on the ability of the PCI method to achieve cell surface expression, which was not previously recognized. Thus the basic PCI technique was well known to the skilled person at the time of the invention. For example, the article by Berg et al. clearly shows that methods for photochemical internalization of molecules were available at the filing date of the application (see, Berg et al., Cancer Research 59: 1180-83 (March 15, 1999), provided herewith in a Supplemental Information Disclosure Statement). In the Berg document, PCI was conducted using a variety of photosensitizers and variety of macromolecules in a variety of different cells. The results were comparable. This therefore illustrates that the basic methods of PCI using various photosensitizers or different cells was well established in the art and should not need to be shown in the present application.
The Examiner has also asserted that the specification lacks teachings on the concentration of photosensitizing agents and the time of illumination for photochemical internalization. However, the Berg article illustrates that useful concentrations and illumination times for photochemical internalization of molecules were available at the filing date of the application. Applicants submit that the Examiner has therefore failed to make a prima facie case that Applicants' specification lacks enablement.

MHC Class I Presentation

The Examiner asserts that the specification does not sufficiently demonstrate that the methods are capable of generating sufficient MHC class I presentation of an antigen to generate an immune response. Claim 2 no longer contains language relating to "class I MHC molecules." Accordingly, this issue is moot.

Example 3 and Figure 4

The Examiner criticizes Example 3 and Figure 4, stating that "the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangle of Figure 4 show a lack of antigen on the surface of the cell." Office Action at page 3. Example 3 describes photochemical internalization of horse radish peroxidase (HRP). Figure 4 is shown below, where the triangles represent the amount of HRP incorporated in cell corpses, the open circles represent the HRP in the cytosol and the closed circles are the total amount of HRP. Hence, we assume that the Examiner is asking why the HRP is mostly present in the cytosol and not associated with the cell corpses (which include the cell membranes).



Applicants submit that the HRP is broken up as described in the specification at page 9, line 32 to page 10, line 7, and HRP antigenic peptides are displayed on the cell surface. Hence, little HRP activity is observed in the cell corpses because they contain essentially only fragments of HRP. Applicants submit that the Examiner has therefore failed to make a prima facie case that Applicants' specification lacks enablement.

Cell Types

The Examiner has stated that the claims are directed to any cell type. However, this is incorrect – claim 2 is directed to use of cancer cells and claims 24 and 38 are directed to antigen-producing cells. Applicants submit that the Examiner has therefore failed to make a prima facie case that Applicants' specification lacks enablement.

Accordingly, the Examiner's allegations are unfounded and the specification clearly enables the subject matter of claims 2, 4, 8-10, 24-34, 37 and 38 and Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

§102 Rejection of the Claims

Claims 2, 4, 6, 8-10, 24-33 and 34 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Application Publication No. WO96/07432 by Berg. The Examiner alleges that WO96/07432 inherently anticipates the invention, that this reference teaches survival of cells after peptide internalization (Abstract) and therefore that this reference encompasses more than internalization of toxins. However, WO96/07432 provides no teaching that falls within the Applicants' claim scope, which requires more than simply the use of a non-toxic molecule with photochemical internalization.

WO96/07432 has very specific disclosures, none of which fall within the scope of the claims. WO96/07432 proposes three types of uses (see pages 7-8). These are (i) cancer treatment in which toxic molecules are internalized to achieve cell death; (ii) gene therapy in which genes are internalized and (iii) experimental methods to introduce molecules into cells in culture *in vitro*. The Examples disclose the internalization of toxic molecules into cells *in vitro* to achieve cell death.

None of these disclosures fall within the scope of the claims. In the case of the use of toxic molecules, as these result in cell death, no presentation of any portion of the internalized molecule is possible as no viable cell remains. Since cell surface presentation is a requirement of all claims, this embodiment falls outside the scope of the claims.

In the embodiment in which genes are internalized, this clearly falls outside the scope of the claims as all claims require the internalization of an antigenic peptide.

In the final embodiment, a variety of molecules may be introduced into cells in culture. However, there is no suggestion that this should be conducted in the presence of immune cells. As such there is no disclosure of the claimed method in which an immune response is generated. Since this is a required feature of independent claims 2 and 24, these claims are novel over this disclosure. Claim 37 is directed to an *in vivo* method in which a patient is treated, and since the final embodiment concerns *in vitro* methods does not deprive this claim of novelty. Claim 38 (as well as claim 24) concerns APCs and nowhere does WO96/07432 suggest use of APCs. Thus all the independent claims and their dependent claims are novel over the specific disclosures of WO96/07432.

The Examiner indicates that the Abstract teaches that cells may survive after peptide internalization. While WO96/07432 may mention use of the PCI method on cells *in vitro* and for gene therapy in which cell death was not contemplated, neither of these embodiments falls with the scope of the claims as discussed above.

Thus, WO96/07432 fails to provide a specific disclosure which deprives any of the claims of novelty. To suggest otherwise is mere hindsight reconstruction by using Applicants' disclosure as a roadmap and construing WO96/07432 out of context. It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391,393 (C.C.P.A. 1965).

For example, Applicants' claim 2 concerns presentation of an antigenic peptide on a cancer cell, subsequent cell surface presentation and generation of CTL mediated killing. WO96/07432 has two disclosures in relation to cancer cells. The Examples provide *in vitro* examples in which some cancer cells are examined, e.g. NHIK3025 and H146. Toxic molecules were applied to these cells, internalized and cell death resulted. The second disclosure teaches that PCI may be used for cancer treatment with toxic molecules being internalized (page 7). The *in vitro* embodiment is outside the claim scope as there is neither cell surface presentation (due to cell death) nor generation of CTL mediated killing since such cells are absent. In the suggested cancer treatment, toxic molecules are used, which again would lead to cell death or would not be

internalized, and in either case, no cell surface presentation would occur. Thus there is no explicit or inherent teaching in WO96/07432 which deprives claim 2 of novelty.

Similar analysis applies to the other claims. Independent claims 24 and 38 refer to antigen presenting cells and there is no disclosure of such cells in WO96/07432. Claim 37 refers to *in vivo* methods and the only explicit disclosure of *in vivo* methods in WO96/07432 relates to cancer treatment or gene therapy, neither of which falls within the scope of claim 37 for the reasons given above. Thus all of these claims are novel as their subject matter is not disclosed in WO96/07432 either explicitly or inherently. The only way one could arrive at the claimed methods would be to modify the teaching and this moves into inventive step considerations and is hence inappropriate.

WO96/07432 is very clear on the methods for which the PCI method may be used, as discussed above. WO96/07432 fails to identify that the PCI method allows cell surface presentation of internalized peptides and hence fails to advocate that the method should be used to stimulate an immune response or that the method should be conducted in the presence of immune cells. The claims which concern either the generation of an immune response or methods suitable for this purpose are thus not taught in this document and withdrawal of this objection is requested.

Applicants therefore submit that the Examiner has failed to prove that WO96/07432 inherently discloses Applicants' invention. Accordingly, withdrawal of this rejection of claims 2, 4, 6, 8-10, 24-33 and 34 under 35 U.S.C. § 102(b), is respectfully requested.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS RCE, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 4th day of May, 2009.

Dawn M. Rode — Dawn M Rode

Name — Signature